Brain Imaging and Behavior (2019) 13:472–481
https://doi.org/10.1007/s11682-018-9862-8

ORIGINAL RESEARCH

Abnormalities in thalamo-cortical connections in patients with first-episode schizophrenia: a two-tensor tractography study

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Published online: 17 April 2018

Abstract

The "cognitive dysmetria" hypothesis suggests that impairments in cognition and behavior in patients with schizophrenia can be explained by disruptions in the cortico-cerebellar-thalamic-cortical circuit. In this study we examine thalamo-cortical connections in patients with first-episode schizophrenia (FESZ). White matter pathways are investigated that connect the thalamus with three frontal cortex regions including the anterior cingulate cortex (ACC), ventrolateral prefrontal cortex (VLPFC), and lateral oribitofrontal cortex (LOFC). We use a novel method of two-tensor tractography in 26 patients with FESZ compared to 31 healthy controls (HC), who did not differ on age, sex, or education. Dependent measures were fractional anisotropy (FA), Axial Diffusivity (AD), and Radial Diffusivity (RD). Subjects were also assessed using clinical functioning measures including the Global Assessment of Functioning (GAF) Scale, the Global Social Functioning Scale (GF: Social), and the Global Role Functioning Scale (GF: Role). FESZ patients showed decreased FA in the right thalamus-right ACC and right-thalamus-right LOFC pathways compared to healthy controls (HCs). In the right thalamus-right VLPFC tract, we found decreased FA and increased RD in the FESZ group compared to HCs. After correcting for multiple comparisons, reductions in FA in the right thalamus- right ACC and the right thalamus- right VLPC tracts remained significant. Moreover, reductions in FA were significantly associated with lower global functioning scores as well as lower social and role functioning scores. We report the first diffusion tensor imaging study of white matter pathways connecting the thalamus to three frontal regions. Findings of white matter alterations and clinical associations in the thalamic-cortical component of the cortico-cerebellar-thalamic-cortical circuit in patients with FESZ support the cognitive dysmetria hypothesis and further suggest the possible involvement of myelin sheath pathology and axonal membrane disruption in the pathogenesis of the disorder.

Keywords Schizophrenia · Thalamus · Tractography · MRI

Hesham M. Hamoda and A. T. Makhlouf contributed equally to this work.

R. W. McCarley died on May 27, 2017 and L. J. Seidman died on September 7, 2017 before the publication of this work was completed.

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Introduction

Schizophrenia ranks among the top ten causes of disability in the world (World Health Organization 2008). Historically, Wernicke, in 1906, proposed that schizophrenia resulted from pathological interactions between different brain regions rather than focal brain abnormalities (Wernicke 1906). Later, Bleuler (1950) introduced the term "schizophrenia" to indicate a breakdown in the association between different mental domains. More recently, the "disconnection hypothesis" brings together Wernicke's suggestion of brain connections being disturbed in schizophrenia, and the symptoms described by Bleuler. This hypothesis describes dysfunctional integration among neuronal systems in schizophrenia (Friston and Frith 1995; Friston 1996; Friston 1998).

Schizophrenia is associated with marked abnormalities in the integrity of myelin sheaths, dysregulation of myelin-associated gene expression, and reduction in number of oligodendrocytes which influence neuronal circuit integrity and eventually signal propagation (Alba-Ferrara and de Erausquin 2013; Roussos and Haroutunian 2014). Such disruptions have been attributed to several factors, including abnormal intrauterine development (Akil and Weinberger 2000) and altered myelination during adolescence (Bartzokis 2002; Flynn et al. 2003). The demyelination hypothesis is further supported by recent studies that demonstrate the role of atypical antipsychotics such as clozapine and quetiapine in myelin lipid synthesis and inhibiting microglial activation (Steiner et al. 2014; Wang et al. 2015).

Currently, the main in vivo method that allows us to study white matter (WM) fiber tracts in the brain is Diffusion Tensor Imaging (DTI). Introduced in 1994, DTI is an MRI technique used to investigate the three-dimensional diffusion of water molecules and makes possible the non-invasive visualization and quantification of WM tracts (e.g., Basser et al. 1994). Since DTI was first applied to schizophrenia (Buchsbaum et al. 1998), hundreds of DTI studies have provided evidence for the disturbance of WM tracts in schizophrenia (see review in Kubicki et al. 2007; see also Kubicki and Shenton 2014).

Andreasen et al. (1998) introduced the "cognitive dysmetria" hypothesis of schizophrenia. This hypothesis suggests that impairments in cognition and behavior in patients with schizophrenia can be explained by disruptions in the cortico-cerebellar-thalamic-cortical circuit (CCTCC). In addition, a "filtering hypothesis" was introduced by Glenthøj and Hemmingsen (1997) to describe abnormal thalamo-cortical information processing in schizophrenia. Such a hypothesis is supported by more recent research that suggests that several thalamic nuclei play a role as signal enhancers (Van der Werf et al. 2003; Sherman and Guillery 2006). Further, abnormalities in the thalamus and its connections with the cortex (Kim et al. 2007; Mitelman et al. 2007), and especially the thalamo-frontal network (Ellison-Wright and Bullmore 2009; Oh et al. 2009), may be linked to the fundamental cognitive deficits observed in this disorder. Other imaging techniques such as fMRI have shown that the aforementioned pathways are affected in individuals with high clinical risk prior to developing psychosis (Anticevic et al. 2015).

Understanding the role of thalamo-frontal connections in schizophrenia is of paramount importance particularly given that many behavioral and cognitive defects are linked to measures of frontal lobe damage (such as spatial working memory deficits, eye tracking abnormalities, Wisconsin Card Sorting Task - see review in Seidman 1983; also Shenton et al. 2001).

More specifically, the ventrolateral prefrontal cortex (VLPFC) plays a role in working memory (Blumenfeld and Ranganath 2006, 2007), abstract thinking (Hoffman et al. 2010), in addition to the mediation of a myriad of cognitive functions that have been found to be abnormal in schizophrenia (e.g., Goldberg and Seidman 1991; Manoach et al. 2000; Weinberger et al. 2001; Boettiger and D'Esposito 2005). Of further note, the anterior cingulate cortex (ACC) is involved in the regulation of emotion and cognition (Bush et al. 2000), in addition to self-awareness and introspection (Goldberg et al. 2006). Moreover, the lateral orbitofrontal cortex (LOFC) contributes to decision-making, emotion regulation, and social functioning (Hooker and Knight 2006).

In this study, we hypothesized abnormalities in WM tracts connecting ACC, LOFC, and VLPFC with their ipsilateral thalamus in patients with first-episode schizophrenia (FESZ) compared to healthy controls (HC). We also investigated whether the hypothesized WM abnormalities correlate with measures of clinical functioning. With respect to the latter, we predicted that functioning scores would be correlated positively with parameters indicating healthier WM tracts, and negatively with parameters indicating impaired WM tracts connecting the thalamus to the three frontal regions.

Methods

Participants

Twenty-six subjects (17 Males, 9 Females) with FESZ and 31 HCs (21 Males and 10 females) were recruited as part of the larger Boston Center for Intervention Development and Applied Research (CIDAR) study (www.bostoncidar.org). FESZ subjects were recruited by referrals from clinicians or through local hospitals and clinics, and HC subjects were recruited through newspaper and website advertisements.

DSM-IV-TR diagnoses were based on interviews with the Structured Clinical Interview for DSM-IV-TR (SCID), Research Version (First et al. 2002a) or the Kid-SCID (Hien et al. 1994) for subjects <18, as well as information from patient medical records. All FESZ subjects met criteria for a

DSM-IV-TR diagnosis for schizophrenia, schizoaffective disorder, or schizophreniform disorder. HCs were drawn from the same geographic base as the FESZ group with comparable age, gender, race and ethnicity, handedness, and parental socioeconomic status (PSES), and were screened for the presence of an Axis I disorder using the SCID DSM-IV, Non-patient Edition (First et al. 2002b). No HCs met criteria for any current major DSM-IV-TR Axis I disorders, or any history of psychosis, Major Depression (recurrent), Bipolar disorder, Obsessive Compulsive Disorder, Post Traumatic Stress Disorder, or developmental disorders. Controls were also excluded for any history of psychiatric hospitalizations, prodromal symptoms, schizotypal or other Cluster A personality disorders, first degree relatives with psychosis, or any current or past use of antipsychotics (other past psychotropic medication use was acceptable, but the subjects must have been off medicine for at least 6 months before participating in the study, except for as needed (PRN) medications like sleeping medications or anxiolytic agents such as beta-blockers for performance anxiety, tremors, etc.).

Exclusion criteria for all subjects were: sensory-motor handicaps, neurological disorders (e.g., epilepsy, traumatic brain injury, defined by loss of consciousness for more than 15 min and/or cognitive/structural sequelae following head trauma), medical illnesses that significantly impair neurocognitive function, diagnosis of mental retardation, education less than 5th grade if under 18 or less than 9th grade if 18 or above, not fluent in English, DSM-IV-TR substance abuse in the past month, DSM-IV-TR substance dependence, excluding nicotine, in the past 3 months, current suicidality, no history of ECT within the past five years for FESZ subjects and no history of ECT ever for HCs, or study participation by another family member. All subjects were screened for foreign metal in their body, pacemakers, pregnancy, claustrophobia or any other circumstance that may pose a risk during MRI scanning.

The study was approved by the local IRB committees at Harvard Medical School, Beth Israel Deaconess Medical Center, Massachusetts General Hospital, Brigham and Women's Hospital and at the Veteran Affairs Boston Healthcare System, Brockton campus. All study participants (or legal guardians for those under 18) gave written informed consent prior to study participation, and subjects received payment for participation.

DTI scanning and processing

Images were acquired on a 3T whole body scanner (General Electric Medical Systems) at Brigham and Women's Hospital, Boston, MA. Diffusion weighted images were acquired with a high-spatial resolution twice refocused echo-planar imaging sequence (TR = 17 s, TE = 78 ms, flip angle 90°, FOV 240 × 240 mm, 85 slices, 1.7 × 1.7 mm in-plane, 1.7 mm slice thickness, 51 gradient directions with b = 900 s/mm 2, and 8 baseline scans with b = 0).

Diffusion weighted images were then corrected for head motion and eddy current distortion by performing an affine registration of each gradient weighted image to the baseline using Brain Extraction Tool (BET) software (Smith 2002).

Region of interest (ROI) acquisition

We used the FreeSurfer software package (version 5.3.0) to parcellate the T-1 weighted structural images into cortical and subcortical gray and white matter regions. Then, using the Nonlinear Image Registration Tool (FNIRT) algorithm in the FSL software, we registered T2 images in the same coordinate space to baseline diffusion weighted images (DWI). The resultant transformation was then applied to T1 segmentation label maps to attain label maps in the coordinate space of the diffusion images (See Fig. 1).

Next, we identified our frontal lobe regions of interest (ROIs): ACC (including its rostral and caudal parts), LOFC, in addition to inferior frontal gyrus (IFG), which consists of parsopercularis, parsorbitalis, and parstriangularis using FreeSurfer parcellations (Desikan et al. 2006). IFG most likely represents the VLPFC (Rygula et al. 2010).

Two-tensor tractography

An unscented Kalman filter (UKF) based two-tensor algorithm that was previously developed in our laboratory (Malcolm et al. 2010a, 2010b) was used to perform whole brain tractography in order to trace fiber tracts throughout the brain (see Fig. 2). The two-tensor technique allows for a higher angular resolution at fiber branching and crossing of fibers than older methods, and thus provides a method for studying complex connections (Malcolm et al. 2010a; Rathi et al. 2011).

We then extracted specific white matter tracts that connected our three target cortical regions of interest to their ipsilateral thalamus (Fig. 3). DTI parameters for every point along the fibers for all selected tracts were then calculated, and averaged over each connection.

Dependent measures in this study were fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD). FA reflects the directional organization of WM tracts in the brain and serves as a measure of WM integrity (Basser and Pierpaoli 1996). FA is a normalized measure of tensor shape, and has a number that lies between 0 and 1. Zero indicates that water molecules diffuse in all directions equally, while a measure of 1 means that diffusion only occurs along one axis. FA can be altered by many micro- and macro-structural changes, including demyelination and/or disruption of axonal membrane (Basser and Pierpaoli 1996), as well as changes in tract organization and coherence. Additionally, in AD and RD, the

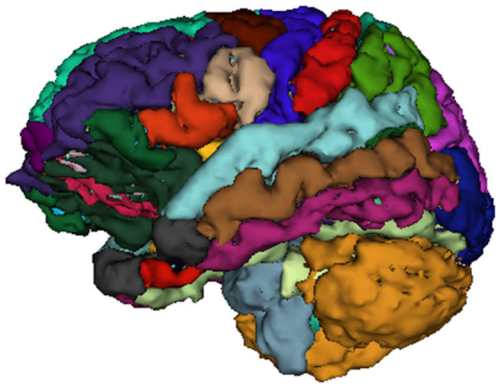

Fig. 1 FreeSurfer parcellation

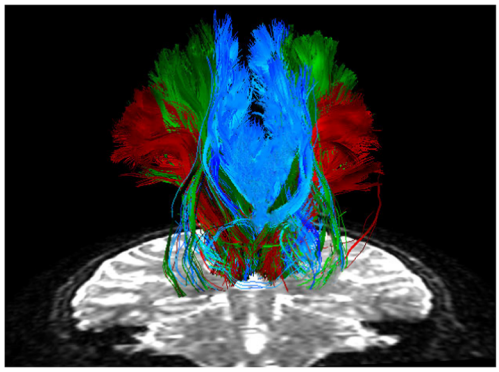

Fig. 3 White matter pathways connecting thalami to ACC (red), VLPFC (green), and LOFC (blue)

diffusion of water along, and perpendicular to the direction of the principal diffusion, is purported to measure axonal and myelin integrity, respectively (Song et al. 2003, 2005).

To ensure that fiber tracts did not overlap and that connections were well defined, we used an FA threshold of <0.15 as our tractography stopping criteria and we only included fibers that had their endpoint on the surface of the desired ROIs.

Statistical approach

The two groups (FESZ and HC) were compared on demographic variables such as gender (Pearson's chi-square test), age, years of education, lifetime alcohol consumption, and history of head trauma complicated by possible brief loss of consciousness (independent samples t-tests).

We then ran an Analysis of Variance (ANOVA) to test for group differences in FA, AD, and RD between the FESZ group and control group. Protected post-hoc independent sample t-tests were used to investigate differences between the two groups. To correct for multiple comparisons we applied a Bonferroni correction (corrected for three tests FA, RD and AD) which adjusted our p value to 0.0167. We also used ANOVA to explore effects of medication status on measures of WM integrity. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS V. 20).

Finally, Pearson correlations were used to evaluate the relationship between measures of WM integrity in the tracts showing significant between-group differences and neuropsychological and clinical test scores.

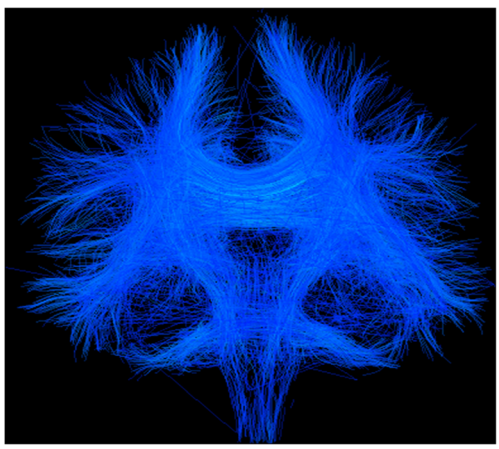

Fig. 2 Whole brain tractography

Results

Demographic data

General demographic data are presented in Table 1. There were no differences in gender ($p = .851$), age ($F_{1,55} = 2.313$, $p = .846$), or years of education ($F_{1,55} = .720$, $p = .255$) observed between the two groups.

Since group matching was done on the aforementioned variables, a finding of no statistical significance was expected.

Moreover, we found no significant differences in lifetime alcohol consumption ($F_{1,55} = 7.404$, $p = .544$) or having a history of head trauma with brief loss of consciousness ($F_{1,55} = .621$, $p = .692$) between our FESZ and HC groups.

Hypothesis-driven comparison of tracts

ANOVA followed by post-hoc independent samples t-tests revealed a significant group effect for the right thalamus- right ACC tract with lower FA in the FESZ group compared to HC ($p = .016$). Similarly, FESZ patients showed lower FA ($p = .032$) in the right-thalamus-right LOFC tract in comparison with HC. Additionally, right thalamus-right VLPC tract showed lower FA ($p = .005$) and higher RD ($p = .027$) in FESZ than in HC. After correcting for multiple comparisons using a Bonferroni correction, however, only the right thalamus- right ACC and the right thalamus-right VLPC tracts were statistically significant.

Table 2 and Figs. 4, 5, 6 and 7 further detail these findings.

Table 1 Demographic characteristics of healthy controls and patients with first-episode schizophrenia

Variable	Healthy Controls		Patients with First-episode Schizophrenia		*p*
	Mean	Range	Mean	Range	
Age (years)	21.75	14–29	21.96	14–32	0.846
Education (years)	14.09	7–17	13.30	7–19	0.255
Gender	N	%	N	%	0.851
Female	10	32.3	9	34.6	
Male	21	67.7	17	65.4	
Race					
Asian	3	9.7	1	3.8	
Black or African American	6	19.4	3	11.5	
White	19	61.3	19	73.1	
Multi-Racial	3	9.7	1	3.8	
Other	0	0	2	7.7	
Head trauma leading to loss of consciousness	4	12.9	4	15.4	
Alcohol consumption	20	64.5	13	50	

Clinical functioning measures

Pearson correlation analysis showed significant correlations between several thalamo-frontal white matter tract connections and clinical functioning measures. Scales for the Global Assessment of Functioning scale (GAF) as well as both the Global Social Functioning (GF: Social) and the Global Role Functioning (GF: Role) Scales showed significant correlations with DTI measures. Functioning scores correlated positively with FA, i.e., FA increases were associated with increased functioning and FA decreases were associated with decreased functioning. Table 3 provides further details.

Discussion

We report findings from the first study of WM pathways connecting the thalamus with specific frontal cortex regions using

Table 2 Independent samples t-tests

Thalamic ROI	Frontal Cortex ROI	Diffusion Parameters	t	*p*
Left thalamus	Left ACC	FA	.902	.371
		AD	.034	.973
		RD	−.481	.632
	Left VLPFC	FA	1.197	.236
		AD	1.828	.073
		RD	.020	.984
	Left LOFC	FA	.225	.822
		AD	.601	.550
		RD	.188	.851
Right thalamus	Right ACC	FA	2.477	**.016**
		AD	−1.715	.092
		RD	−1.881	.065
	Right VLPFC	FA	2.911	**.005**
		AD	.982	.330
		RD	−2.273	.027
	Right LOFC	FA	2.199	.032
		AD	.070	.945
		RD	−1.379	.173

Statistically significant following Bonferroni correction for multiple comparisons

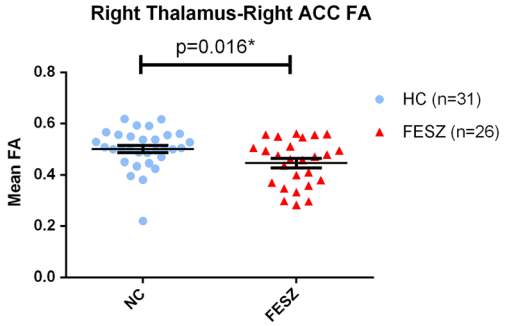

Fig. 4 Right thalamus- Right ACC pathway FA. * Statistically significant following Bonferroni correction for multiple comparisons

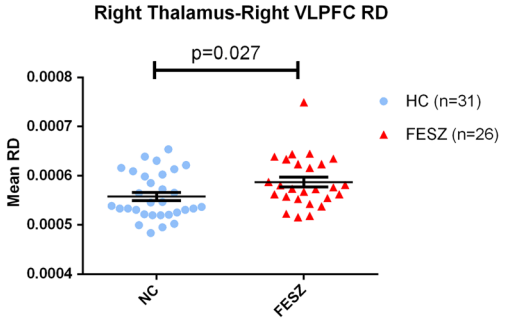

Fig. 6 Right thalamus- Right VLPFC pathway RD

a novel method of two-tensor tractography in patients diagnosed with FESZ compared to HCs.

Two-tensor tractography was used because it is a relatively new approach to tractography that overcomes the challenge of crossing and branching fibers that affects single tensor tractography. Using a tractography approach that is able to incorporate crossing and branching fibers is important, particularly given that it is estimated that as many as 90% of white matter voxels contain crossing fibers (Jeurissen et al. 2013).

As hypothesized, our results suggest a disruption in the integrity of WM tracts connecting the frontal lobe and thalamus. Additionally, statistically significant correlations between WM abnormalities and clinical as well as functioning measures were found.

More specifically, we found decreased FA in the FESZ group compared to HCs in the right thalamus- right ACC tract and in the right thalamus-right VLPC pathway.

Several factors contribute to tractography parameters including axonal integrity, degree of myelination, and fiber arrangements (Alba-Ferrara and de Erausquin 2013). Decreased FA in the aforementioned pathways is hypothesized to signify demyelination and/or disruption of axonal membrane (Basser and Pierpaoli 1996).

Such indications of disruption in right thalamus- right ACC and the right thalamus-right VLPC pathways are also supported by correlations with measures of clinical functioning. In particular, reductions in FA were associated with lower global functioning scores as well as lower social and role functioning scores (See Table 3).

Our findings of clinical correlations with tractography findings provide additional evidence for the cognitive dysmetria hypothesis. In our case, disruptions in the thalamic-cortical component of the cortico-cerebellar-thalamic-cortical circuit are related to impairments in functioning.

Changes in parameters signifying pathology in pathways connecting thalamus to frontal cortex regions responsible for regulation of cognition and emotion (like ACC) and playing a role in working memory (VLPFC) in addition to correlations with symptoms and functioning scores represent additional evidence for the involvement of these frontal areas in schizophrenia.

While abnormalities in WM integrity were found in both hemispheres, findings that reached statistical significance were only found in the right hemisphere. We hypothesize that such lateralization is attributed to the fact that our subjects are in the early stage of the disease and it is possible that disruptions become more pervasive with disease progression as more disturbances in the trajectory of myelin development ensue. A recent study from our group supports our aforementioned hypothesis in other tracts. Seitz et al. (2016) showed that patients in the early course of the disease exhibit lower FA and higher RD in the right arcuate fasciculus, cingulum bundle, and inferior longitudinal fasciculus compared to normal subjects. The pattern of alterations found in our study in patients with FESZ has been previously reported in studies of thalamo-frontal connections in patients with *chronic* schizophrenia. For example, Kubota et al. (2013) found lower FA in WM fibers connecting thalamus and the right orbitofrontal cortex in patients with chronic schizophrenia compared to healthy controls. Additionally, another study

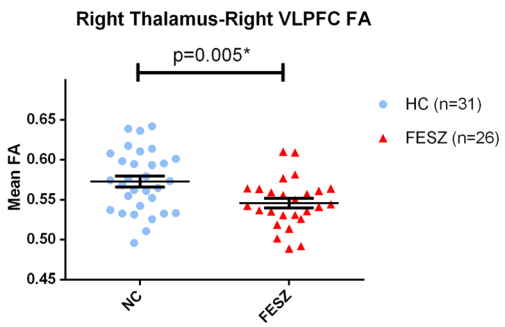

Fig. 5 * Statistically significant following Bonferroni correction for multiple comparisons. Right thalamus- Right VLPFC pathway FA

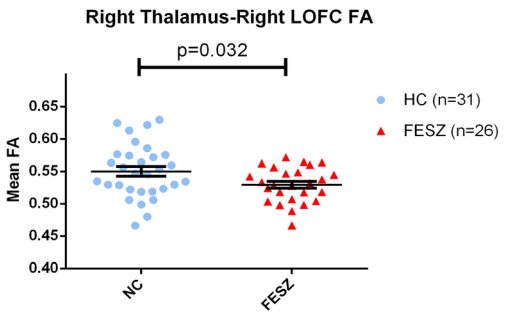

Fig. 7 Right thalamus- Right LOFC pathway FA

Table 3 Pearson correlation analysis

Clinical test		Tract	r	*p*
GAF	Current GAF score	Right ACC FA	.302	**.023**
		Right VLPFC FA	.266	**.045**
	Highest GAF score in the past year	Right ACC FA	.339	**.012**
		Right VLPFC FA	.367	**.006**
GF: Social	Social functioning at baseline	Right ACC FA	.008	.952
		Right VLPFC FA	−.068	.620
	Lowest Social Functioning in the past year	Right ACC FA	.232	.088
		Right VLPFC FA	.345	**.010**
	Highest Social Functioning in the past year	Right ACC FA	.139	.315
		Right VLPFC FA	.162	.241
GF: Role	Role functioning at baseline	Right ACC FA	.223	.099
		Right VLPFC FA	.364	**.006**
	Lowest role functioning in the past year	Right ACC FA	.354	**.008**
		Right VLPFC FA	.512	**.000**
	Highest role functioning in the past year	Right ACC FA	.250	.066
		Right VLPFC FA	.387	**.004**

from our group (Oh et al. 2009) found that FA was decreased in ACC projections as well as in VLPFC projections. Our study supports the notion that these disruptions are not only present in chronic schizophrenia but also in its earlier stages.

While no previous studies have examined WM connections between thalamus and specific frontal lobe areas in *first-episode* schizophrenia using two tensor tractography, a study by our group investigated thalamo-cortical connectivity using probabilistic tractography. Cho et al. (2015) revealed that connectivity between thalamus and orbitofrontal cortex is reduced in patients with first episode schizophrenia in comparison to healthy volunteers. Moreover, several studies have investigated the anterior limb of internal capsule, anterior thalamic radiation, and anterior corona radiata. Such pathways are believed to contain thalamo-frontal fibers. One study found gender-based variation in FA parameters of the anterior limb of internal capsule. Male patients had exhibited FA in the right hemisphere but slightly lower FA in the left anterior limb of internal capsule. However, female patients showed lower FA on the right and higher FA on the left side (Schneiderman et al. 2009). Another study by Wang et al. (2013) showed significant decrease in FA in the white matter around the ACC bilaterally and the right anterior corona radiata of the frontal lobe in patients with first-episode schizophrenia compared to healthy volunteers. A more recent study revealed that patients with first-episode schizophrenia evinced lower FA and higher RD compared to healthy volunteers in the left anterior thalamic radiation (Zang et al. 2016). On the other hand, Lee et al. (2012) found no significant differences in FA in either the right or left anterior limb of internal capsule in patients with first-episode psychosis.

In summary, previous studies of pathways containing thalamo-frontal fibers in first-episode schizophrenia have found conflicting results. This discrepancy could be attributed to the cross-sectional nature of the above-mentioned studies given that schizophrenia is a progressive disease in at least a subset of patients. Other possible explanations include studying large WM pathways that contain several tracts and the difference in methodology between studies (tract-based spatial statistics vs. one-tensor vs. two-tensor tractography). Also, none of these studies used two tensor tractography which allows for a higher angular resolution at branching and crossing of fibers.

Limitations

This study is limited by its cross-sectional nature. Longitudinal studies are needed to follow patients with FESZ for a longer time period and to investigate the trajectory of myelin development.

Technical limitations of our study that require further investigation include the effect of third ventricle cerebrospinal fluid and thalamic perforating micro-arterial feeds on anisotropy of neighboring white matter (Aung et al. 2013) in addition to the impact of body mass index on parameters including FA (Stanek et al. 2011) and AD (Kullmann et al. 2016) in patients with FESZ compared to healthy controls.

Conclusions

This is the first study to use two-tensor tractography in FESZ to investigate connections between thalamus and specific frontal cortex areas suspected to play a role in the pathophysiology of schizophrenia. The current data support our hypothesis of aberrant thalamo-cortical WM pathways being present

in the early stages of schizophrenia and the presence of significant associations between DTI parameters and clinical functioning measures. Such findings of WM alterations and clinical correlations at the onset of schizophrenia further support the cognitive dysmetria hypothesis of schizophrenia and suggest the possible involvement of myelin sheath pathology and axonal membrane disruption in the pathogenesis of the disorder.

Acknowledgements The authors would like to thank Laura Levin-Gleba, BS, Xue Gong, BA, Dominick Newell, BA, and Anni Zhu, BA for their support as research assistants. We also thank the clinical, research assistant, and data management staff from the Boston CIDAR study, including: Caitlin Bryant, BS, Ann Cousins, PhD, APRN, Grace Francis, PhD, Molly Franz, BA, Michelle Friedman-Yakoobian, PhD, Lauren Gibson, EdM, Anthony J. Giuliano, PhD, Andréa Gnong-Granato, MSW, Maria Hiraldo, PhD, Sarah Hornbach, BA, Matcheri Keshavan, MD, Kristy Klein, PhD, Grace Min, EdM, Corin Pilo, LMHC, Janine Rodenhiser-Hill, PhD, Julia Schutt, BA, Rachael Serur, BS, Shannon Sorenson, BA, Reka Szent-Imry, BA, Alison Thomas, BA, Chelsea Wakeham, BA, and Kristen A. Woodberry, MSW, PhD, Finally, we are grateful for the hard work of many research volunteers, including, Devin Donohoe, Zach Feder, Sylvia Khromina, Alexandra Oldershaw, Elizabeth Piazza, Julia Reading, and Olivia Schanz.

Funding Source This study was supported by NIH P50MH080272 (LJS, JMG, RWM, MES, NM, RMG, JW), R01MH102377 (MK, MES, YR), R01MH097979 (YR), VA Merit Awards (RWM, MES), The Commonwealth Research Center (SCDMH82101008006, RMG, LJS, JW), and a VA Schizophrenia Center Grant (RWM, MES). This work was also supported by the Dupont-Warren, Livingston and Shore Fellowships from the Harvard Medical School, a Faculty Development Fellowship from Boston Children's Hospital (HMH), a NIH/NIMH T32 MH 016259-29 Stuart T. Hauser Clinical Research Training Program in Biological and Social Psychiatry NIH P50MH080272 (JF). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

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